

In 8.0 ml of tetrahydrofuran were suspended 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the suspension was stirred in an argon atmosphere at 0 to 5° C. To this solution, the above lithium diisopropylamide solution was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20° C. for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate=2:1) to give 124 mg of tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate (yellow oil) in 6% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 1.48 (9H, s), 2.668–2.83 (2H, m), 3.0–3.8 (2H, bs), 3.42 (2H, s), 4.02–4.17 (2H, m), 4.40 (1H, m)

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 27.8, 45.7, 51.0, 65.6, 68.0, 82.3, 166.4, 203.4

#### Example 10

##### Tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate

Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5° C. and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 3.0 mL of tetrahydrofuran were dissolved 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5° C. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred at 5° C. for 50 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes and the mixture was further stirred at 5 to 20° C. for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

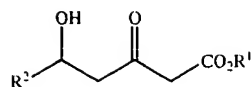
The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate=2:1) to give 980 mg of tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate (red oil) in 48% yield.

#### INDUSTRIAL APPLICABILITY

The present invention, constituted as described above, enables the production of 5-hydroxy-3-oxopentanoic acid derivatives, which are of use as pharmaceutical intermediates, particularly intermediates of HMG-CoA reductase inhibitors, from inexpensive, readily available starting compounds at a non-very-low temperature.

What is claimed is:

1. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R<sup>1</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R<sup>2</sup> represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy-carbonyl group.

which comprises permitting a lithium amide of the following formula (III):



(III)

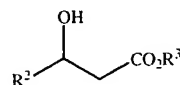
wherein R<sup>4</sup> and R<sup>5</sup> may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below -20° C.:



wherein R<sup>1</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:

(II)



wherein R<sup>2</sup> represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy-carbonyl group; R<sup>3</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R<sup>2</sup> and R<sup>3</sup> may be joined to each other to form a ring.

2. The process according to claim 1

wherein, referring to the lithium amide, R<sup>4</sup> and R<sup>5</sup> each represents an isopropyl group.

3. The process according to claim 1

wherein, referring to the acetic acid ester, R<sup>1</sup> represents a tert-butyl group.

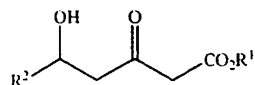
4. The process according to claim 1,

wherein a magnesium halide is added in permitting the lithium amide to act.

5. The process according to claim 4

wherein magnesium chloride is used as the magnesium halide.

6. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):

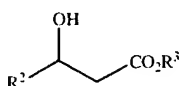


wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy carbonyl group,

which comprises treating a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):

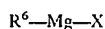


wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



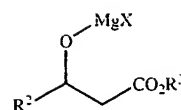
wherein  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy carbonyl group;  $R^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  and  $R^3$  may be joined to each other to form a ring,

with a Grignard reagent of the following formula (V):



wherein  $R^6$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents halogen,

to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):



wherein  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy carbonyl group;  $R^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms;  $R^2$  and  $R^3$  may be joined to each other to form a ring; and X represents a halogen atom,

and permitting a lithium amide of the following formula (III):



wherein  $R^4$  and  $R^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group

to act upon the mixture at a temperature not below  $-20^\circ\text{C}$ .

7. The process according to claim 6

wherein, referring to the lithium amide,  $R^4$  and  $R^5$  each is an isopropyl group.

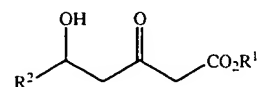
8. The process according to claim 6

wherein, referring to the acetic acid ester,  $R^1$  represents a tert-butyl group.

9. The process according to claim 6,

wherein, referring to the Grignard reagent,  $R^6$  represents a tert-butyl group and X represents a chlorine atom.

10. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy carbonyl group,

which comprises permitting a lithium amide of the following formula (III):

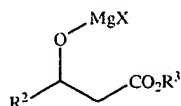


wherein  $R^4$  and  $R^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below  $-20^\circ \text{C}.$ :



wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



wherein  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy carbonyl group;  $R^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12

carbon atoms and an aralkyl group of 7 to 12 carbon atoms;  $R^2$  and  $R^3$  may be joined to each other to form a ring; and X represents a halogen atom.

11. The process according to claim 10

wherein, referring to the lithium amide,  $R^4$  and  $R^5$  each represents an isopropyl group.

12. The process according to claim 10

wherein, referring to the acetic acid ester,  $R^1$  represents a tert-butyl group.

13. The process according to claim 10,

wherein, referring to the compound (VI), X represents a chlorine atom.

14. The process according to claim 1

wherein  $R^3$  is a methyl group or an ethyl group.

15. The process according to claim 1

wherein  $R^2$  is a chloromethyl group, a cyanomethyl group or a benzyloxymethyl group.

16. The process according to claim 1

wherein  $R^2$  and  $R^3$  are joined to each other to form a methylene group.

17. The process according to claim 1

wherein the compound (II) or (VI) is optically active.

18. The process according to claim 2

wherein, referring to the acetic acid ester,  $R^1$  represents a tert-butyl group.

19. The process according to claim 2

wherein a magnesium halide is added in permitting the lithium amide to act.

20. The process according to claim 3

wherein a magnesium halide is added in permitting the lithium amide to act.

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